REMARKS

Favorable reconsideration of this application in view of the remarks to follow and allowance of the claims of the present application are respectfully requested.

In the Official Action, Claims 1-3, 5-9, 13-15 and 24-30 are rejected under the sole ground of 35 U.S.C. §103(a) as obvious over Cozzi et al.(WO 98/04525) in view of Cortes et al. *Investigational New Drugs* 18: 57-82, 2000.

Specifically, the Examiner contends that Cozzi et al. teach the acryloyl distamycin derivative of formula I and Cozzi et al. disclose that the acryloyl distamycin derivatives can be combined with an additional antitumor agent for treating cancer or for ameliorating the conditions of mammals, including humans, suffering from cancer. Further, the Examiner admits that Cozzi et al. do not teach a protein kinase inhibitor. However, the Examiner contends that Cortes et al., the secondary reference, teach that CGP 57148 (ST1571) is a novel agent that inhibits the tyrosine kinase activity of ABL, and that clinical results suggest a very potent anti-leukemia activity with minimal toxicity in patients with Interferon-resistant Ph-positive CML. Further, the Examiner contends that, generally, it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose. Thus, the Examiner asserts that combining the acryloyl distamycin compounds of Cozzi et al. with the ST1571 of Cortes et al. would achieve the compositions and methods of the present invention since they are both taught to be useful for treating leukemia.

Further, with respect to the term "synergistic antineoplastic effect" as presently claimed, the Examiner contends that such term is defined in the specification (page 8, lines 1-4) as "the inhibition of the growth of the tumor, preferably the complete regression of the tumor, by

administering an effective amount of the combination comprising an acryloyl distamycin derivative of formula (I) and a PK inhibitor to mammals, including humans." In view of such definition, the Examiner contends that the artisan would reasonably expect inhibition of the growth of leukemia or regression of leukemia from the administration of the acryloyl distamycin compounds of Cozzi and the ST1571 of Cortes, since they both are useful for treating leukemia.

In view of the above remarks, and in connection with the *in vitro* biological data submitted to the Examiner as "Exhibit 1" in applicants' response dated November 7, 2007[1], which shows the synergistic effect (i.e. more than additive effect) of the presently claimed composition, it appears that the Examiner recognizes the synergistic effect of the presently claimed composition, but simply objects to applicants' own definition of "synergistic effect" because such definition does not seem to exactly reflect the ordinary meaning of "synergistic effect", which is the more than additive effect. Therefore, it appears that the instant rejection is more of an issue of formality where the Examiner expects applicants to use an appropriate language in the claim to reflect the synergistic effect possessed by the presently claimed composition.

In response, applicants have amended the claims in a manner as shown above. Specifically, applicants have introduced appropriate verbiage in the claims to capture the synergistic effect (i.e. more than additive effect) possessed by the presently claimed composition, product and method. Support of the amendment is found at the specification, at page 9, the last

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[1] Since the Examiner has a copy of Exhibit 1, applicants do not resubmit it in this response. However, for the convenience of the Examiner, applicants summarize the synergistic effect as follows:
"Study of three combinations is presented in Exhibit 1. The combinations are, respectively, the combination of brostallicin (an α-bromo- or α-chloro-acryloyl-distamycin derivative of formula (I)) with ST1571 (a protein kinase inhibitor) on K562 human CML cell lines; the combination of brostallicin with ZD1839 (a protein kinase inhibitor) on human lung cancer NCI-H322M human lung cancer cell line, and the combination of brostallicin with OSI-774 (a protein kinase inhibitor) on MDA-MB-468 human breast carcinoma cell line. The *in vitro* data shows that, on human tumor cells, brostallicin can be combined effectively with each of the above-identified three protein kinase inhibitors to produce a synergistic effect (i.e. more than additive effect)."

paragraph where it describes "[a]s the effect of an acryloyl distamycin derivative of formula (I) and a PK inhibitor is significantly increased without a parallel increase of toxicity, the combined therapy of the present invention enhances the antitumoral effects of the acryloyl distamycin derivative and of the PK inhibitor and, hence, provides the most effective and least toxic treatment for tumors." Since no new matter is introduced into the originally filed application, entry thereof is respectfully requested.

In view of the above remarks, applicants submit that the claims, as presently amended, are not obvious over the applied references because the applied references, either alone or in combination, do not teach or suggest that the presently claimed composition, product or method has an antitumoral effect more than the additive antitumoral effect of the acryloyl distamycin derivative and the protein kinase inhibitor, which is fully supported by the data presented in Exhibit 1 as submitted along with applicants' response to U.S. Patent & Trademark Office dated November 7, 2007.

In view of the above remarks, applicants submit that the instant rejection has been obviated. As such, reconsideration and withdrawal of the instant rejection is respectfully requested.

In view of foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

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